OPTIMIZATION OF TECHNIQUE FACTORS FOR A SILICON DIODE ARRAY FULL-FIELD DIGITAL MAMMOGRAPHY SYSTEM AND COMPARISON TO SCREEN-FILM MAMMOGRAPHY WITH MATCHED MEAN GLANDULAR DOSE

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Contrast-detail image analysis was performed to optimize technique factors for detection of low-contrast lesions using a silicon diode array full-field digital mammography (FFDM) system under the conditions of matched mean glandular dose (MGD) across the full range of compressed breast thicknesses. FFDM results were compared to screen-film mammography (SFM) at each breast thickness.

Four contrast-detail (CD) images were acquired on a SFM unit with optimal techniques at 2, 4, 6, and 8 cm breast thicknesses. The MGD for each breast thickness was calculated based on HVL and entrance exposure measurements on the SFM unit. A computer algorithm was developed to determine FFDM mAs that matched MGD between FFDM and SFM at each thickness, while varying target, filter, and kVp across the full range available for the FFDM unit. CD images were then acquired on FFDM for kVp values from 23-35 for Mo-Mo, 23-40 for Mo-Rh, and 25-49 for Rh-Rh under the constraint of matching the MGD from screen-film for each breast thickness (2, 4, 6, and 8 cm). CD images were scored independently for SFM and FFDM at each technique by 6 readers. CD scores were analyzed to assess trends as a function of target-filter and kVp and were compared to SFM at each breast thickness.

For 2 cm thick breasts, optimal FFDM CD scores occurred at the lowest possible kVp setting for each target-filter and were not significantly different from SFM CD scores. FFDM CD scores decreased as kVp increased for each target-filter under the constraint of matched MGD. For 4 cm breasts, the optimum FFDM CD score was superior to the SFM CD score and decreased as kVp increased for each target-filter combination. For 6 cm breasts, optimum FFDM CD scores were significantly higher than SFM CD scores while decreasing slightly as kVp increased for Mo-Mo, but not varying significantly as a function of kVp for either Mo-Rh or Rh-Rh. For 8 cm breasts, optimum FFDM CD scores were significantly higher than SFM CD scores. For Mo/Mo and Rh/Rh, FFDM CD scores increased significantly as kVp increased.

These results indicate that low-contrast detection was optimized for FFDM by using a softer x-ray beam for thin breasts and a harder x-ray beam for thick breasts when MGD was kept constant for a given breast thickness.

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MAMMOGRAM SCREENING BY AUTOMATED FOLLOW-UP: MAMMOGRAM MODELING

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This work is concerned with the problem of detecting early cancerous changes by comparing temporal sequences of mammograms of a same patient. The view taken in this work is that the precise mammogram comparison is intractable due to the differences between the images arising from differences in compression and positioning. In order to get a better insight into effects of compression and positioning, the later phase of the project focused on modeling breast tissue and mammographic examination and generating synthetic mammograms that can provide insights into effects of positioning and compression on appearance of mammograms.

The synthetic mammogram generation comprises of: (1) modeling breast anatomic structures, (2) modeling breast tissue compression, and (3) modeling X-ray image acquisition. The breast structures are modeled based on their anatomic properties obtained from description in literature and histologic slice images. The 3-D tissue model consists of regions of predominantly adipose tissue (AT) and predominantly fibroglandular tissue (FGT), with realistically distributed anatomic structures: adipose compartments, Coopers ligaments, and breast ducts. The model of breast compression includes deformation of the large-scale anatomic structures using realistic values of tissue elasticity and force. The acquisition model assumes parallel beam x-ray propagation without scatter. The appropriate values of linear x-ray attenuation coefficients are associated with each simulated tissue structure.

The models were validated by comparing complexity of obtained texture patterns with those in real mammograms. By varying the size of model structures, we have matched the average properties of clinical mammogram texture and the range of features seen over a large group of mammograms. The best match was achieved for the simulated adipose compartments with radii of 4-13.3 mm in AT region and radii of 2.7-5.33 mm and 1.3-2.7 mm in the retroareolar and dense FGT, respectively. The conclusion of the validation study was that the developed simulation methods can be used for development, testing, and optimization of imaging techniques and for comparison of imaging modalities with potential to improve screening reliability.

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THE MODULATION TRANSFER FUNCTION (MTF) OF CRT DISPLAY SYSTEMS

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We investigate methods to derive the Modulation Transfer Function of CRT display systems, a performance parameter which is strictly defined only for linear systems. Elements of linear system theory were applied to the evaluation of the non-linear CRT display system by using the small-signal approximation and derive the MTF. A CCD Camera was used in the data acquisition by recording test images displayed by the CRT. This paper presents a comparison of three methods to derive the MTF.

MTFs were derived from: (1) square wave response; here small-amplitude square waves of different spatial frequencies are displayed on a uniform background in horizontal and vertical direction. The Fourier Transforms of the data recorded by the camera and representing the square wave response of the display, provide the output modulations of the fundamental sine wave and their harmonics; (2) horizontal and vertical, positive single-line profiles; here a single line is displayed on the CRT with uniform background at a luminance close to that of the line; the MTF is found from the 1-D Fourier Transform of the line profiles and corrected by the width of the actual input line; (3) white noise transfer (broad-band response); here simulated white spatial noise is displayed; the standard deviation of the amplitude comprises a small portion of the luminance range but is large compared to that of the CRT spatial noise; the MTF is derived from the resulting Noise Power Spectrum; the induced Noise Power Spectrum of course falls off like the squared MTF of the CRT.

The measurements were made on a high-performance monochrome CRT with a maximum luminance level of approximately 500 cd/m^2 and a pixel matrix of 2048 horizontally * 2560 vertically. MTFs derived from the three methods are almost equal. The method of the broad band response is the most elegant one, but is the most labor intensive one: The Noise Power Spectra need to be measured and averaged many times, and it is difficult to remove the CRT raster completely.

We propose to use line profiles when routinely estimating the MTF of CRT systems. Using a CCD camera for the data acquisition results in high accuracy and precision in the respective performance characteristics.

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COMPUTERIZED CRT SNR MEASUREMENTS: EFFECT OF PHOSPHOR TYPES

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We compared the image quality of two Siemens 5Mega Pixel CRT displays for mammography, one with a P-45 phosphor and the other with a P-104 phosphor, both calibrated according to the DICOM standard for a maximum luminance of 500 Cd/m2. Images (512 x 512 x 8 bits) of computer generated test-patterns were digitized by a CCD camera at a magnification of 8, resulting in 1316 x 1036 x 14 bit image files. The CCD images were analyzed by the template-correlation method suggested by Tapiovaara and Wagner (TW), yielding signal-to-noise ratio (SNR) estimates for the test patterns.

The patterns consisted of targets superposed on uniform backgrounds and uniform fields. Three background values were used with DDL values of 55, 127 and 200, and each uniform field was imaged 15 times by the CCD camera. Each signal image consisted of 25 identical targets, each consisting of a periodic array of target elements, which were dots or horizontal or vertical line-segments. The pixel value difference between the target and the background was varied systematically, as was the spacing between the target elements. Templates were constructed in the manner described by TW except that a special alignment technique was used to account for the scan lines. In all 162 target containing CCD images and 45 uniform field images (for each monitor) were analyzed using the non-prewhitening ideal observer template of TW with a zero frequency filter.

For each test-pattern type and spacing, the dependence of SNR on target contrast was non-linear, and could be well fitted with a 2-parameter exponential rise-to-maximum function, thereby allowing the identification of low-contrast and high-contrast SNR values. For high-contrast signals the P-45 phosphor did better than P-104, except at the highest luminance, where the reverse was true. For low-contrast signals the performance of the two monitors was almost identical across the entire luminance range.

It should be noted that the TW method yielded precise (~2%) SNR measurements quite independent of any assumptions about the MTF, NPS or pixel intensity distribution. We believe this method is ideally suited to the evaluation of the new AMLCD devices that are becoming available, whose evaluation presents special problems to conventional linear system analysis.

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AUTOMATED ANALYSIS OF MAMMOGRAPHIC BREAST DENSITY FOR BREAST CANCER RISK ESTIMATION

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Mammographic breast density, an indicator of the proportion of fibroglandular vs. fatty tissue in the breast, has been found to have strong correlation with breast cancer risk. Mammographic breast density has therefore been used for monitoring the response in studies of preventive or interventional treatment of breast cancer. Breast density changes during the course of treatment are often estimated visually on mammograms by radiologists; which involves large inter- and intraobserver variations. The goal of this project is to develop an automated image analysis method that can provide a more consistent and reproducible estimate of the percent dense breast area on a mammogram.

An automated computer program has been developed that performs breast density analysis using the following steps: detection of the breast boundary, reduction of the image dynamic range, analysis and classification of the shape of the gray level histogram, adaptive gray level thresholding, and estimation of the percent dense tissue area relative to the breast area. The performance of the algorithm was evaluated by comparing the computer segmentation results to manual segmentation with interactive thresholding by five radiologists.

To further investigate the relationship between the mammographic breast density and the amount of fibroglandular tissue in the breast, the image analysis program was applied to the mammograms of 37 patients who had corresponding magnetic resonance (MR) images of the breasts. The fibroglandular tissue regions in the MR slices were segmented interactively with a user interface, and the percentage of fibroglandular tissue volume in the breast estimated. The correlation between the percent dense area estimated from mammograms and the percent volumetric fibroglandular tissue estimated from MR images was studied.

We found that the correlation between the computer-estimated percent dense area and the average of the five radiologists' manual segmentation was 0.94 and 0.91, respectively, for CC and MLO views, with a mean bias of less than 2%. The percent breast dense area of the CC and MLO views has a correlation of 0.92 and 0.91, respectively, with the percent volumetric fibroglandular tissue on MR images. Mammographic density is therefore highly correlated with the volumetric fibroglandular tissue in the breast, indicating its usefulness as a surrogate for breast density estimation.

The computerized image analysis tool is useful for breast density estimation on mammograms. The automated analysis is expected to contribute to the understanding of the relationship of mammographic density to breast cancer risk, detection, and prognosis, and to the prevention and treatment of breast cancer.

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DEVELOPMENT OF DIGITAL STEREO IMAGING TECHNIQUE FOR MAMMOGRAPHY

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One of the limitations of mammographic imaging is that overlapping dense tissue in the breast can camouflage true lesions or create false lesions in the projected image. The goal of this project is to develop a digital stereoscopic imaging technique for mammography. It is expected that overlying dense tissues will be separated from the lesion in the stereoscopic views, thereby increasing the conspicuity of the lesion, and that the ability to analyze the 3-dimensional (3D) distributions and shapes of lesions such as calcifications and masses can potentially improve the accuracy of mammographic interpretation by radiologists and reduce unnecessary biopsies.

We have investigated the dependence of depth discrimination on imaging parameters including the stereo angle, x-ray exposure, magnification, and display zoom. Image display software was developed for a high-quality stereo viewing station. Observer studies were conducted to view stereo images of 3D mammographic phantoms acquired under various imaging conditions. The accuracy of the observers in differentiating the relative depths of two overlapping fibrils was evaluated. In addition, we have developed 3D virtual cursors for measurement of the depth of objects in a stereomammogram. The effects of imaging parameters and virtual cursor shapes on depth measurement accuracy have been studied.

It was found that the accuracy of depth discrimination increased with increasing stereo angle, exposure, and fibril depth separation. Zooming the contact stereo images by 2X did not improve the accuracy. Under conditions of high noise and small depth separation between the fibrils, depth discrimination was significantly better in stereo images acquired with geometric magnification than in images acquired with a contact technique and displayed with or without zooming. Magnification mammography also provided the highest accuracy for depth measurement with a virtual cursor, whereas display zoom did not improve accuracy.

These studies indicate that stereoscopic imaging, especially with magnification, may be useful for differentiating overlapping tissues from masses on mammograms and visualizing the spatial distribution of microcalcifications in a cluster, thereby improving the accuracy of mammography for breast cancer detection and diagnosis.

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HIGH-RESOLUTION LOW-DOSE DIGITAL MAMMOGRAPHIC DETECTOR USING HEAVY SCINTILLATOR AND EFEBCCD

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We have set up, at the Mass General Hospital, a prototype of a high-resolution low-dose digital X-ray device initially for clinical application in stereotactic needle breast biopsy and localization procedures, where real time imaging is essential. High quality "snapshot" of the area of interest will enable the radiologist to place the needle much faster and more accurately than with film guided techniques. This would reduce the discomfort to the patient as it will improve the precision of the location and reduce the procedure time.

This detector consists of a 80μm -thick X-ray converter of density 8g/cm^3, directly coupled to the 8cm diameter input fiber optic (FO) window of an electrically focusing electron bombarded CCD detector (EFEBCCD) with 1k x 1k pixels. Unique features are: 1) this high-density X-ray converter is only 80 μm thick and has a stopping power (quantum efficiency) of about 93% for 20 KeV X-rays; 2) EFEBCCD can map a large image area to a small CCD without loss of signals and amplify signals without amplifying the CCD or electronic noises. We characterized the detector performance using phantoms: S/N, DQE, MTF and LSF resolution.

The measured detective quantum efficiency (**DQE**) of the complete system is **80%** for the prototype in contrast with the 20% typical efficiency of film mammographic devices, and the measured MTF values for this prototype are: **MFT= .9, .5, and .2 at 2, 6, and 8 lp/mm** spatial frequencies respectively, significantly better than those of standard mammography.

Software is developed for detector performance.

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NEW TRANSFER THEORY RELATIONSHIPS FOR SIGNAL AND NOISE ANALYSES OF X-RAY DETECTORS

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X-ray mammography is the most reliable method available at present for the detection of breast cancer in screening programs, although it still does not detect all cancers. A great deal of research effort over the past several decades has therefore been directed towards the development of better and more effective detector designs for use in x-ray mammography. In particular, several new digital technologies are being developed in various laboratories around the world that show great promise. Theoretical models of the detective quantum efficiency (DQE) of these systems are required to provide insight into fundamental performance limitations and to provide benchmarks for the evaluation of measured system performance.

We have shown that the simple "cascaded" approach can be extended for use with complex models of real systems by the use of parallel cascades. A theoretical expression for the cross spectral density of quantum point processes, the quantity required for the use of parallel cascades, has been developed. These enable comprehensive models to be developed of detector performance that include the effect of characteristic x-ray reabsorption.

A theoretical model of the DQE for a CsI-based flat-panel detector is developed that includes the effect of secondary quantum noise, noise aliasing and x-ray reabsorption. This is the first theoretical frequency-dependent model that includes all these effects and shows excellent agreement with experiment.

It is shown that even for this "indirect" detector, noise aliasing reduces the DQE by as much as 50%, but only very close to the sampling cut-off frequency. Secondary quantum noise is a small effect only if sufficient optical coupling exists between the phosphor and active matrix detector. Results suggest that this coupling may be be as good as is generally claimed by detector manufacturers, and may be the single most important factor resulting in future improvements of flat panel detectors. X-ray reabsorption can reduce the DQE by 20-25% over a wide range of spatial frequencies. This is an important observation for the development of optimal exposure techniques and may limit the expectation that patient dose can be reduced with digital detectors by the use of increased x-ray energy.

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AUTOMATIC EXPOSURE CONTROL DEVICE FOR DIGITAL MAMMOGRAPHY

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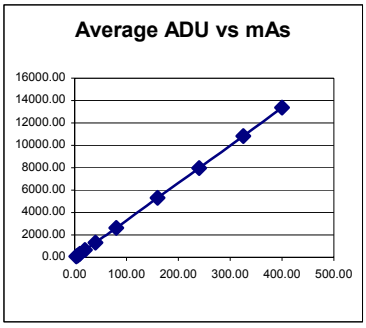
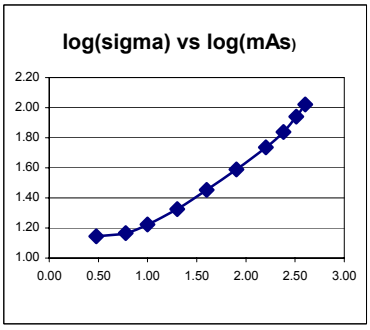
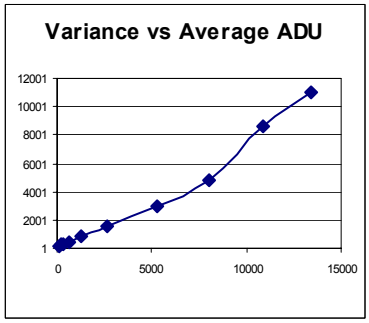
The broad, long-term objective of this IDEA proposal is to achieve optimized image quality for DM within acceptable limits of radiation exposure by developing innovative approaches for controlling DM exposures. We have developed analysis tools to evaluate the effect of radiographic heterogeneity on the selection of an "Exposure-Controlling Region Of Interest" (ECROI) and have performed analysis of digital mammograms of patients with a variety of compositions and breast sizes. We then calculated ratios of root mean square signal to root mean noise for patients with a variety of breast compositions (radiodensity). The total variance in the ECROI, the portion of the variance that is due to noise, and the ratio of the RMS signal to the RMS noise were calculated. These ratios suggest the approximate magnitude of the target SNR values to be used in the AEC algorithm.



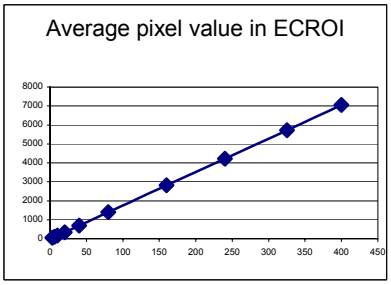
Linearity as a Function of X-ray Exposure

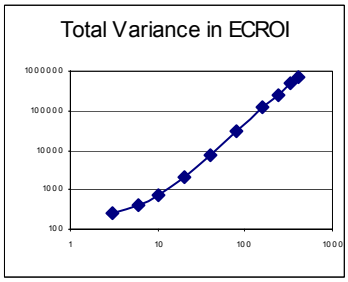


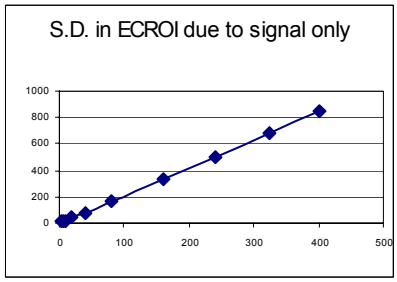
Log of the SD vs. log of the mAs



Variance vs. Average ADU







These results demonstrate that the total variance in the ECROI is the arithmetic sum of the signal and noise variances. Therefore, determination of the total variance at any given mAs, along with the known noise variance at that mAs, permits calculation of the SNR for all mAs values. In the context of AEC development, this means that we can quickly assess the RMS signal variance in the ECROI following pre-exposure at low mAs, and extrapolate to the target mAs value that will result in the desired SNR.

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CLINICAL EVALUATION OF DIGITAL MAMMOGRAPHY

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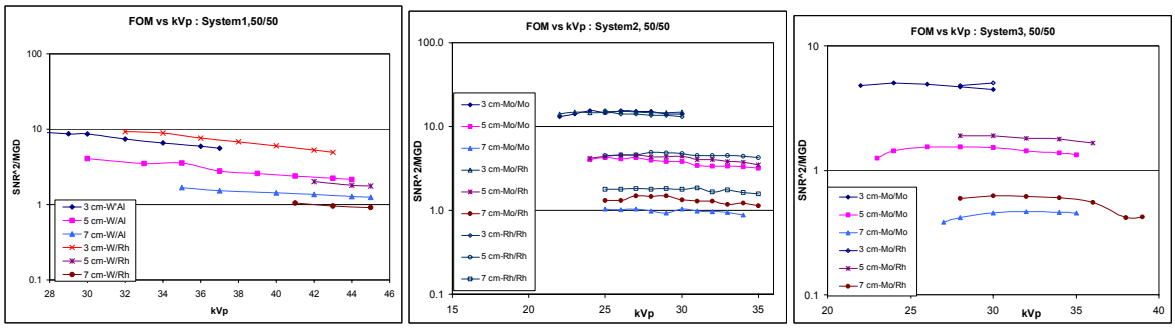
The investigations being conducted under this DAMD award involve a multi-institutional group of physicists and clinical researchers who have previously collaborated to establish a research group known as the International Digital Mammography Group. Our study entails two aspects of translational research related to the clinical application of digital mammography: technology optimization and a clinical evaluation. The DM units of three different manufacturers were valuated using a common set of phantoms was circulated between the participating institutions. Image analysis on each system included: beam optimization. Calculations of signal-to-noise ratio and mean glandular breast radiation dose. For the data reported here, the test objects of interest were two stepwedges, one each of calcification equivalent and mass equivalent material. The mass equivalent stepwedge has the same x-ray attenuation as 100% glandular equivalent material, and the microcalcification equivalent step wedge is composed of calcium carbonate.



The second phase of this project is a multi-center clinical evaluation comparing optimized digital mammography to SFM in women with moderate or marked breast density who present for problem-solving mammography. Because the dynamic range of x-ray signals recorded with standard screen-film mammography systems is greatly exceeded by digital systems, one of the most promising contributions of digital mammography is improved imaging of moderate to markedly dense breast tissue. Women consenting to participate will undergo a 4-view screen-film and digital mammogram. Three groups of woman are being recruited: (1) Group 1: palpable breast lesion scheduled for biopsy, (2) Group 2: non-palpable lesion detected on SFM and scheduled for biopsy, and (3) Group 3: non-palpable lesion detected on SFM and scheduled for diagnostic imaging and mammographic follow-up only. The primary outcome of interest—lesion detectability on digital versus screen-film mammograms—will be evaluated based on a receiver operating characteristic curve analysis of readers' assessments of the likely presence of malignant lesions based on mammographic findings. Secondarily, differences in case management between the two imaging modalities will be measured.

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AUTOMATED STEREO SPOT MAMMOGRAPHY FOR IMPROVED IMAGING OF DENSE BREASTS

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One of the primary limitations of present day x-ray mammography screening is the poor detectability of cancers within dense breasts. Even the new digital mammography systems will not completely solve this problem. We are developing a novel automatic stereo spot technique for improved imaging with the digital mammography systems. The basic idea is to automatically detect any suspicious dense region within the full-field digital mammogram, and within seconds take a stereo digital mammogram of only that region using automated collimation, manual x-ray tube shift, and more penetrating exposures.

Software was developed to allow radiologists to trace suspicious dense regions within mammograms, and an observer study was performed to assess the agreement of the selected regions. Prototype devices were designed and built to automatically collimate the beam to the selected region and position a spot compression paddle at that region. Experiments were performed with breast-simulating phantoms to compare combined spot compression and collimation to spot collimation with stereoscopic image acquisition.

Ratios of the intersections to unions of the selected regions were computed for each set of 2 radiologists. Combining the results for all sets, the averages of the largest ratios ranged from 28%-46% (mean 37%+/-6%). The averages of the second largest ratios ranged from 6%-16% (mean 10%+/-3%). Corresponding values for the reproducibility of regions selected by individual radiologists were 43%-59% and 15%-27%. For the phantom study, an in-house developed 3-D virtual cursor was used to measure the separations between overlapping simulated masses in stereoscopic images obtained with and without spot compression. Spot compression was found to reduce the spacing between the masses. The improved visualization of overlapping tissues with stereoscopic imaging and reduced complexity in system design and operation caused us to favor and pursue developing stereo imaging with spot collimation.

It is anticipated that automated stereo spot mammography will significantly improve the detection and characterization of masses in dense breasts in routine screening and will therefore improve the accuracy of screening programs.

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DESIGN OF A MULTISITE, TELEPHONE-BASED TELEMAMMOGRAPHY SYSTEM

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As the number of mammographic examinations increases, it becomes clear that due to shortages of expert mammographers in many locations, combined with the desire to make it convenient for the patient to undergo the procedure, there may be need for high-quality telemammography systems that enable a distributed acquisition-centralized expert review type solution to the problem. The relatively high recall rates (5-15%) of screened women to supplement information that had not been ascertained during the initial visit (e.g., magnification views) also make it desirable to enable physician "monitoring" and "management" of remote locations so that at least some clinical and diagnostic decisions can be made while the patient remains in the clinic. It is the purpose of this project to develop, test, and evaluate a telemammography system that will operate between several remote locations and a large breast cancer center. The system has been designed, assembled and tested for technical performance and reliability. Currently the three remote sites are located anywhere from 15-90 miles away from our hub in Pittsburgh, PA. The remote sites are all outpatient clinics, which are staffed by a physician from one day a week to half a day every two weeks. Cases from multiple sites have been transmitted simultaneously and received at the hub. To date we have received over 300 cases from the remote sites, and we are analyzing user functionality at all locations. The system digitizes a mammogram at 50 micron pixel size, segments the breast tissue depicted on the image, compresses the resulting image file (~50:1), and transmits it over a telephone line to the central site where the data are received, decompressed, and displayed on a high-resolution workstation in approximately 4 minutes per image. Initial assessment of image quality at the receiving site indicates that the images are of diagnostic quality and automatically set display parameters are rated "acceptable" to "outstanding" in over 75 percent of cases. Basic utility of the workstation is satisfactory. We are currently performing large multi-site retrospective assessment as to the possible use of such a system in reducing recall rates. The technical specifications for a multi-site telemammography system have been met. The use of this concept for remote management of cases in underserved areas is in its initial evaluation stages. We also plan to explore the advantages and limitations of incorporating CAD results into the system for improved decision making at the central location (time wise, effectiveness, or accuracy).

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DOSE AND IMAGE QUALITY IN DIGITAL MAMMOGRAPHY

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The purpose of this study was to investigate the image quality and absorbed dose characteristics of a commercial digital mammography imaging system, and to identify an optimal x-ray tube voltage for imaging simulated masses.

Images were taken of an ACR accreditation phantom using a LORAD digital mammography system. In one experiment, exposures were performed at 80 mAs with x-ray tube voltages varying between 24 and 34 kVp. In a second experiment, the x-ray tube voltage was kept constant at 28 kVp and the technique factor was varied between 5 and 500 mAs. The average glandular dose at each x-ray tube voltage was determined from measurements of entrance skin exposure and x-ray beam half value layer. Image contrast was measured as the digital signal intensity difference for the image of a 4 mm thick acrylic disk. Image noise was obtained from the standard deviation in a uniformly exposed region of interest.

The measured digital signal intensity was proportional to the mAs and to the kVp^5.8. Image contrast was independent of mAs, and dropped by 21% when the x-ray tube voltage increased from 24 to 34 kVp. At a constant x-ray tube voltage, image noise was shown to be approximately proportional to (mAs)^(-0.5). At 80 mAs, increasing the x-ray tube voltage from 24 to 34 kVp increased the CNR by 78%, and increased the average glandular dose by 285%. At a constant lesion CNR, the lowest average glandular dose value occurred at 27.3 kVp.

These results show that imaging simulated masses in a 4.2 cm compressed breast at ~27 kVp results in the lowest average glandular dose. These results will help to optimize the clinical use of digital mammography whereby patient doses are kept as low as reasonably achievable with no loss of diagnostic information.

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GENERATING A 3D VIEW OF THE BREAST FROM THE TWO STANDARD MAMMOGRAPHIC PROJECTIONS

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The purpose of this feasibility study was to generate a three dimensional (3D) view of the breast from its two standard mammographic views, i.e., the cranio-caudal (CC) and medio-lateral (ML) or medio-lateral-oblique (MLO) views, that will also include a 3D representation of mammographically identified lesions. The hypothesis was that a 3D representation of the breast and breast lesions might increase the physician's ability to characterize and differentiate them.

Phantom and patient data were used to test our 3D reconstruction methodology. The CIRS phantom models 13 and 51 were initially used. Digital images of the phantoms were acquired with the GE Senographe 2000D digital mammography system (GE, Milwaukee, WI). CC and MLO images were recorded of the phantoms with and without reference markers. The purpose of the reference markers was to provide additional reference points to improve the registration of the two views as required for the 3D reconstruction. Different markers were evaluated at various locations on the phantoms' surface. Markers included N, A, and O spots (Beekley, Bristol, CT). CIRS model 51 was the phantom that best represented clinical breast imaging and was the one further used in our tests. A set of patient data was also used in the initial development and testing. Digitized film mammograms and direct digital mammograms were also evaluated that contained calcification clusters and/or masses, the location and size of which were identified on both the CC and ML or MLO views by expert mammographers.

The 3D reconstruction algorithm consisted of several modules: (1) Breast segmentation, i.e., separation of the breast area from the image background. (2) Pectoral muscle segmentation, i.e., separation of the pectoral muscle from the breast area in the ML or MLO views. (3) Selection of reference points for the registration of the two views. When there were no markers, the nipple was the only reference point. (4) Registration and alignment of the segmented breast areas from the CC and ML or MLO views. (5) Estimation of the uncompressed breast and its surface points. (6) Insertion of lesion in the 3D breast maintaining its size and location. A user-friendly interface was developed using Interactive Data Language (IDL) (Research Systems Inc., Boulder, CO) widgets that interfaced all processing modules and displayed a 3D image of the breast that could be rotated in both the vertical and horizontal directions with lesion color changing with change in depth.

In this preliminary work, we successfully generated a 3D representation of the phantoms and clinical cases with associated lesions with a relatively high degree of accuracy in terms of breast volume and lesion location. The use of reference markers at known locations on the surface of the breast can significantly improve reconstruction accuracy as suggested by the reconstruction of phantom images with and without markers. Further studies are needed to determine the right location for the markers and the minimum number of markers necessary for accurate 3D reconstruction.

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OPTIMAL COLOR FOR SUPRATHRESHOLD AND THRESHOLD CONTRAST PERCEPTION IN FLAT PANEL DISPLAYS

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Today the most color present in a radiographic film is dye (generally blue) in film base added to reduce eyestrain for the interpreting radiologist. The photopic response of the human eye is maximized for a photon wavelength of about 500 nm and decreases for higher and lower wavelengths. With the rapid development of digital image acquisition and displays systems there has arisen the possibility of creating purely color-scale radiographic images. Especially this is a very desirable for new flat-panel display technologies, such as active-matrix liquid crystal display (AM-LCD) or active-matrix organic light-emitting display (AM-OLED). In addition, the signal acquired by a mammography flat panel detector can contain up to 12 bits of image data. It is known that the human eye cannot discern between more than 10 bits of data in a monochrome mode. Therefore, part of the information acquired by the X-ray digital detector is lost.

We investigated the effect of the monochrome color scale on contrast sensitivity of the AM-LCD. We have initially concluded that the perception of supra-threshold contrast was superior for monochromatic scales in the blue-green region of the spectrum. Later, we used an alternative method to validate those observations. We performed an analysis of the variations in the contrast threshold for five color scales that showed promise at supra-threshold levels. We used targets with same physical contrast with 0.25 line-pair/mm at the same luminance for all five scales. The targets were surrounded by uniform backgrounds (10 by 10 cm) at approximate the average luminance and color coordinates of the sinusoidal circular pattern having a diameter of 100 pixels (about 2 cm). We computed the differences in contrast threshold by fitting a psychometric function to data obtained with eight observers, and by calculating the contrast with a detection probability of 0.5 and 0.85. We find that the contrast threshold for green scales is in average 20% smaller than for the rest of the scales.

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THREE-DIMENSIONAL HISTOPATHOLOGY

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The mammary gland is a complex, highly heterogeneous organ. Understanding normal mammary gland development and its neoplastic, tissue level deviations (i.e., breast cancer) requires looking the mammary gland as a whole, integrating both morphological and molecular information in three-dimensions. Most analytical methods in biology ignore this, in that they extrapolate information obtained from isolated cells taken outside their native tissue environment, or use limited morphological information obtained by looking at a few two dimensional sections of a three dimensional volume.

We have developed a computer assisted three-dimensional microscopy system that allows semi-automatic acquisition, annotation, reconstruction and molecular analysis of fully sectioned thick tissue samples [1]. The system is controlled by an in-house developed client-server application, which can be executed over a local area network (LAN) and can run on multiple hardware platforms.

To show the use of the system, we reconstructed four mouse mammary glands. Two animals were euthanized and their inguinal glands extracted, one embedded in paraffin (PF) and the other one put in OCT and kept frozen (FR). All glands where fully sectioned at 5 microns. PF glands were H&E stained. FR glands were alternatively stained with H&E or immunostained for the receptors of estrogen (ER alpha) and progesterone (PR). All ducts were annotated in both PR glands, and then fully reconstructed in 3D. Selected ducts and terminal end buds were annotated in the images of the sections of the FR glands, reconstructed, and then the distribution of receptor positive cells automatically calculated in different parts of the mammary gland.

Our study shows the feasibility of this type of whole-gland three-dimensional analysis, which can now be applied to a plethora of developmental and breast cancer studies that require looking at the molecular or genetic characteristics of the cells without losing sight of the tissue environment where they reside.

[1] A System for Combined Three-Dimensional Morphological and Molecular Analysis of Thick Tissue Specimens. Fernandez-Gonzalez R., Jones A., Garcia-Rodriguez E., Chen P.Y., Idica A. , Barcellos-Hoff M.H., Ortiz-de-Solorzano C. In Press, Microscope Research and Technique.

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THREE-DIMENSIONAL CHARACTERIZATION OF DUCTAL CARCINOMA IN SITU OF THE BREAST

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The etiology of ductal carcinoma in situ of the breast (DCIS) is one of the most controversial issues in breast cancer research. Existing studies suggest but can not completely prove genetic and temporal relationships between DCIS and precursor (hyperplasia) or product (invasive carcinoma) lesions. Under that scenario, DCIS would represent one step during the clonal progression of the disease. If that is the case, assuming that a complete clonal replacement is very unlikely to occur, we hypothesize that a systematic, cell-by-cell, 3D morphological reconstruction of DCIS specimens should reveal both morphological and genetic connections with both pre-neoplastic and invasive tumor components.

To reconstruct DCIS lesions, we have developed a computer assisted three-dimensional microscopy system that allows acquisition, annotation, reconstruction and molecular analysis of fully sectioned thick tissue samples [1].

We reconstructed two paraffin-embedded DCIS tissue blocks containing extended comedo-type DCIS as well as both morphologically normal and invasive carcinoma areas. Both blocks were sectioned at 5 microns, every 20 microns of tissue. Sections were alternatively stained with H&E or counterstained and in situ hybridized (FISH) with a probe to the erbB2 gene. Only erbB2 positive samples were used.

DCIS tumors, normal ducts and invasive areas were annotated and reconstructed in 3D using the H&E sections. Morphological connections between them were defined. Finally, the cell-by-cell level of erbB2 amplification was calculated in different parts of the DCIS lesion and compared with that of normal and invasive areas.

In the cases we have studied, we have not found morphological connections between the DCIS and either normal or invasive carcinomas, and we have found different levels of amplification both within and between DCIS and normal and invasive tissue. However we consider our results preliminary. More and larger specimens must be analyzed before extracting general conclusions.

[1] A System for Combined Three-Dimensional Morphological and Molecular Analysis of Thick Tissue Specimens. Fernandez-Gonzalez R., Jones A., Garcia-Rodriguez E., Chen P.Y., Idica A. , Barcellos-Hoff M.H., Ortiz-de-Solorzano C. In Press, Microscope Research and Technique.

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NEW HIGH-RESOLUTION DISPLAY FOR DIGITAL MAMMOGRAPHY WORKSTATIONS

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According to the National Institutes of Health, Digital Mammography is one of the most promising research areas for improving early detection of breast cancer; however, current display systems remain an impediment to full realization of its potential (1).

We have been studying how to improve the resolution of cathode ray tubes (CRTs) so that they can meet what has been available from X-ray film. In a cathode ray tube display, an electron beam is scanned in raster fashion over a phosphor screen. The current in the beam is modulated to produce the desired light output pattern. Because of the low mass of electrons it is easy to deflect electron beams. It is much harder to additionally preserve the ability to finely focus the beam after deflection. There are two ways to deflect an electron beam - using magnetic fields or electric fields. The vast majority of CRT displays use magnetic deflection. The basic advantage of magnetic deflection is that deflection aberrations are lower by a factor of 2 or 3 compared to electric field deflection. A way to significantly reduce electric field deflection aberrations would be an important development.

This has recently been accomplished – initially according to calculations (2) and now verified by experimental results (3). With this improvement, we intend to prototype an 8 megapixel, 300 microamp beam current CRT with electric field deflection. This will be an improvement over what is currently available from any CRT. Using this display in digital mammography workstations will likely help radiologists identify malignancies and ignore benign lesions.

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DUAL-ENERGY DIGITAL MAMMOGRAPHY— SIGNAL-TO-NOISE ANALYSIS AND INVERSE MAPPING TECHNIQUES

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X-ray mammography continues to be the major tool for screening and diagnostic examinations of breast cancer. In mammography, the presence of microcalcification clusters together with their shape and size, often constitute an indication for breast cancer. However, microcalcifications are often obscured by overlapping tissue structures. The long-term goals of our research are to develop and investigate dual-energy digital imaging techniques to separate the calcifications from tissue structures and enhance their detection and visualization.

Under these goals, we have performed a signal-to-noise ratio (SNR) analysis to estimate the noise level in the dual-energy calcification signals relating it to the breast thickness, tissue composition, scintillating material, and kVp. Distribution of the exposure between low and high energy images was optimized to maximize the resulting calcification SNR. It was found that optimal calcification SNR was obtained by using 25 and 50 kVp for low and high energy x-rays, and using CsI(Tl) as a scintillating material compared to gadolinium-oxysulphide. Calcification SNRs were computed, assuming a cubic shape, for various breast thickness and composition and used in conjunction with the Rose criteria to estimate the smallest detectable calcification size.

We have also investigated inverse-mapping techniques to estimate tissue composition and calcification thickness from separately acquired low and high energy images. Calibration data was acquired using an aSi:H/CsI(Tl) flat-panel based mammography unit for various material/thickness combinations under narrow beam geometry at 25 and 49 kVp. The calibration data were fit to inverse functions for mapping the measured transmission into tissue composition and calcification thickness. Two practical scenarios for dual-energy imaging were investigated: (1) breast density measurements without the need for breast compression; and (2) microcalcification imaging with varying tissue composition under breast compression. The rms uncertainties, not including the noise in the raw images, in the model predictions are: (1) 0.5 mm for tissue thickness and 2% glandular for tissue composition; and (2) 50 microns for Al thickness and 5% glandular for tissue composition.

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A NEW PIXEL DETECTOR FOR SECOND-GENERATION DIGITAL MAMMOGRAPHY

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Digital mammography is a technique that uses a digital detector to record the image in a mammography examination where the image is then processed and displayed on a computer. It offers advantages by facilitating applications such as computer-aided detection (CAD), electronic file archiving, and tele-mammography, which can provide quality services to remote or underserved communities. Compared to films, it has advantages in image contrast, dynamic range and detective quantum efficiency (DQE). First-generation digital mammography systems, which are based on a scintillator technology, are commercially available. However, this technology still suffers inefficiencies such as sub-optimal DQE and possibly MTF. We are developing a new solid-state GaAs detector using Semi-Insulating (SI) and thick epitaxial GaAs materials. These new detectors, which directly convert x-rays into charge signals, can overcome the inefficiencies of the first-generation digital systems. This may provide improved detectability of subtle tumors, which have slight density differences compared to other breast tissues, as well as and tiny micro-calcifications.

Our first batch of fabricated SI GaAs detectors showed low responses to x-rays. Further analysis of these samples showed that some contamination during the detector fabrication process might have caused the low x-ray response. Devices from a second batch from which the contamination problem was eliminated showed much improved charge collection efficiency, with signals approximately ten times better than in the earlier ones. The electric field in these devices also penetrated the wafer thickness. Using x-rays from an ^{241}Am source, the charge collection efficiency (CCE) for the refined GaAs detectors was measured to be about 40%. This CCE value was still lower than desired. It was limited by the small $\mu\tau$ product within the SI GaAs material, and thus the charge transport was adversely affected. The restricted $\mu\tau$ value observed in SI GaAs was a result of deep-level traps in the material, predominantly the arsenic-antisite EL2 vacancy defects.

We subsequently shifted our attention to GaAs materials with low charge trapping. It appears that an epitaxial growth method may provide material with suitable charge transport properties. This technique is capable of yielding thick (~0.5mm) single crystal GaAs wafers. We have recently successfully grown such thick expitalxial GaAs materials and also fabricated test sample detectors from them. A room temperature photoluminescence image of the sample shows much improved uniformity of the epitaxial GaAs material compared to that of the SI ones. Gamma ray and alpha particle spectra were also measured. Our new data show much improved performance on these new detectors and the results will be presented.

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HIGH-UNIFORMITY CDZNTE DETECTORS FOR DIGITAL MAMMOGRAPHY

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Mammography has attained widespread acceptance as an important tool for the screening and diagnosis of breast cancer. Digital mammography is a technique that uses a digital detector to record the image in a mammography examination where the image is then processed and displayed on a computer. It offers advantages by facilitating applications such as computer-aided detection (CAD), electronic file archiving, and tele-mammography, which can provide quality services to remote or underserved communities. Compared to films, it has advantages in image contrast, dynamic range and detective quantum efficiency (DQE). First-generation digital mammography systems, which are based on a scintillator technology, are commercially available. However, this technology still suffers inefficiencies such as sub-optimal DQE and possibly MTF. We are developing a new x-ray detector using high uniformity CdZnTe materials grown from Low Pressure Bridgman (LPB) method. This new detector, which directly converts x-rays into charge signals, can overcome the inefficiencies of the first-generation digital systems. This may provide improved detectability of subtle tumors, which have slight density differences compared to other breast tissues, as well as tiny micro-calcifications.

We have studied CdZnTe materials grown from High Pressure Bridgman (HPB) method and obtained good results from small size samples made of HPB materials. We also found that the sealed high pressure and high temperature crystal growth environment of the HPB method could not yield large crystal grain sizes. The LPB CdZnTe material, on the other hand, can yield high uniformity, large size single crystals. The LPB CdZnTe material has just become available commercially. Therefore, our first task is to study the surface characteristics of these new LPB CdZnTe materials. Our first batch sample detectors were fabricated with LPB CdZnTe material from Yinnel Tech Inc., using a fabrication process developed for commercial HPB CdZnTe materials. These samples were put in an x-ray machine where their x-ray responses under various bias conditions were measured. The $\mu\tau$ products were also obtained from the data, which agreed with our expectations. Preliminary spectra with a ^{241}Am source were also obtained, which showed good energy resolutions. A sample detector was also hybridized to our MARY ASIC CCD readout chip using the same fabrication technique for HBP CdZnTe materials. Some local leakage spots were observed in a flooded x-ray imaging test.

Our next step is to develop a customized electrode fabrication process for this new LPB CdZnTe material. This task is in progress. Our objective is to minimize the electrode leakage and maximize the charge collection efficiency. So far we have performed infrared transmission measurements on the <111> oriented LPB CdZnTe samples. Surface polishing and electrode deposition for a few samples are also underway. The new detectors will be characterized and the results will be presented.

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